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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

FORMAN, BETTY J

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 03/26/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/335,218

Applicant(s)

WRIGHT ET AL.

Examiner

BJ Forman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 January 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-61 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

1. This action is in response to papers filed 11 January 2002 in Paper No. 19 in which claims 1 and 55 were amended and claim 62 was canceled. All of the amendments have been thoroughly reviewed and entered. The Objection to Claim 55 is withdrawn in view of the amendments. The previous rejections in the Office Action of Paper No. 17 dated 13 July 2001 under 35 U.S.C. 103(a) are withdrawn in view of the amendments and new ground for rejection. All of the arguments have been thoroughly reviewed but are deemed moot in view of the withdrawn rejections and new ground for rejection. The arguments are discussed below as they apply to the new grounds for rejection. New grounds for rejection are discussed.

The examiner's Art Unit has changed from 1655 to 1634. Please address future correspondence to Art Unit 1634.

Currently claims 1-24 and 55-61 are under prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 1-5, 7-19, 24, 55-57 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of

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Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696) and Krausa et al (Human Immunology, 1995, 44: 35-42).

Regarding Claim 1, Newton et al. disclose a method for detecting a single nucleotide polymorphism in a target comprising: hybridizing a detector primer to the target, wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide polymorphism which is a 3' terminal nucleotide of the detector primer (Column 4, lines 31-67); determining efficiency of the detector primer extension; and detecting the presence or absence of the single nucleotide polymorphism based on the efficiency of the detector primer extension (Column 13, lines 11-34) wherein the amplification reaction is an isothermal reaction (Column 7, lines 50-60) and wherein the diagnostic nucleotide is a 3' terminal nucleotide (Column 4, lines 31-67) but they do not teach the diagnostic nucleotide is about one to four nucleotides from the 3' terminal nucleotide of the primer and they do not teach the method comprises a second primer such that extension of the second primer displaces the detector primer. However, second primers which upon extension displace a detector primer (i.e. Strand Displacement Amplification (SDA)) was well known in the art at the time the claimed invention was made as taught by Walker et al. Specifically, Walker et al. teach a method similar to that of Newton et al. for detecting a target comprising: hybridizing a detector primer and a second primer to the target such that extension of the second primer displaces the detector primer, displacing the detector primer from the target by extension of an upstream primer and amplifying the target (page 1692, Fig. 1) wherein displacement by extension of the second primer generates target sequence of defined 3' and 5' ends with increased efficiency and decreased non-specific primer binding (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detector primer extension of Newton et al. by also extending an upstream primer to displace the detector primer for the expected benefits of increased efficiency and decreased non-specific product formation as taught by Walker et al. (Abstract) to thereby efficiently and accurately detect a single nucleotide polymorphism.

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Additionally, diagnostic primers comprising diagnostic nucleotides adjacent to the 3' terminal nucleotide was well known in the art at the time the claimed invention was made as taught by Krausa et al. Specifically, Krausa et al teach a diagnostic primer comprising a diagnostic nucleotide about one to four nucleotides from the 3' end (Tables 2A and 2B) wherein the primers are complementary to polymorphic sites and are useful for identifying specific polymorphic sites and fine mapping of the polymorphism (page 38, left column, lines 8-20). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the diagnostic nucleotide and diagnostic primer taught by Krausa et al to the diagnostic primers of Newton et al and to design diagnostic primers having a diagnostic nucleotide about one to four nucleotides from the 3' terminal nucleotide of the diagnostic primer based on known locations of a polymorphism as taught by Krausa et al for the obvious benefits of polymorphism-specific detection and complete polymorphism mapping as taught by Krausa et al (page 38, left column, lines 8-20).

Regarding Claim 2, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using the detector primer i.e. the primer is extended only when the terminal nucleotide of the primer is complementary to the target (Column 12, lines 47-59).

Regarding Claim 3, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using multiple detector primers comprising different diagnostic nucleotides (Column 30, Example 1).

Regarding Claim 4, Newton et al. teach the method wherein two detector primers are used to identify which of two possible alleles is present in the target sequence (Column 30, Example 1).

Regarding Claim 5, Newton et al. teach the method wherein four detector primers are used to identify the nucleotide present in the target sequence at the position of the single nucleotide polymorphism (Column 32, Example 4).

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Regarding Claim 7, Newton et al. teach the method wherein the detector primer further comprises a nucleotide which forms a nondiagnostic mismatch with the target sequence (Column 12, lines 22-26).

Regarding Claim 8, Newton et al. teach the method wherein the nondiagnostic nucleotide is positioned within fifteen nucleotides of the diagnostic nucleotide in the detector primer (Column 12, lines 27-32).

Regarding Claim 9, Newton et al. teach the method wherein the nondiagnostic nucleotide is positioned 1-5 nucleotides from the diagnostic nucleotide in the detector primer (Column 12, lines 27-32).

Regarding Claim 10, Newton et al. teach the method wherein the nondiagnostic nucleotide is adjacent to the diagnostic nucleotide in the detector primer i.e. 1, 2 or 3 bases from the terminal nucleotide (Column 12, lines 27-32).

Regarding Claim 11, Newton et al. teach the method wherein the detector primer is about 15-36 nucleotides long (Column 11, lines 12-20).

Regarding Claim 12, Newton et al. teach the method wherein the detector primer is about 18-24 nucleotides long (Column 11, lines 12-20).

Regarding Claim 13, Newton et al. do not teach the method comprising a second primer. However, Walker et al. teach the similar method wherein the second primer is an amplification primer for use in an amplification reaction (page 1692, left column first full paragraph and Fig. 1). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single primer amplification of Newton et al. by also using a second upstream amplification primer for the expected benefit of enhanced amplification of single-stranded or double-stranded targets as taught by Walker et al. (page 1695, left column, last paragraph-right column first paragraph).

Regarding Claim 14, Newton et al. teach the method is an isothermal amplification reaction (Column 7, lines 50-60) but they do not teach the reaction is selected from SDA, 3SR,

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NASBA and TMA. However, Walker et al. teach the similar method wherein the reaction is SDA (Abstract) wherein the SDA method eliminates temperature cycling, permits amplification under high stringency conditions and amplifies low-abundance targets (page 1695, right column last full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the isothermal amplification method of Newton et al. with the SDA method of Walker et al. for the expected benefits of SDA taught by Walker et al. i.e. permits amplification under high stringency conditions and amplifies low-abundance targets (page 1695, right column last full paragraph) to thereby specifically amplify a rare single nucleotide polymorphism.

Regarding Claim 15, Newton et al. teach the method wherein the detector primer is about 12-50 nucleotides long (Column 11, lines 12-20).

Regarding Claim 16, Newton et al. teach the method wherein the detector primer is about 12-24 nucleotides long (Column 11, lines 12-20).

Regarding Claim 17, Newton et al. teach the method wherein the detector primer is about 12-19 nucleotides long (Column 11, lines 12-20).

Regarding Claim 18, Newton et al. teach the method wherein the presence or absence of the single nucleotide polymorphism is detected by means of a label associated with the detector primer (Column 14, lines 40-48).

Regarding Claim 19, Newton et al. teach the method wherein the label becomes detectable upon extension of the detector primer (Column 8, lines 13-23).

Regarding Claim 24, Newton et al. teach the method wherein the efficiency of detector primer extension is determined quantitatively i.e. detection of heterozygous or homozygous samples (Column 13, lines 35-41).

Regarding Claim 55, Newton et al. teach a method for detecting a single nucleotide polymorphism in a target sequence comprising: hybridizing to the target sequence a detector primer comprising a diagnostic nucleotide for the single nucleotide polymorphism which is a 3'

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terminal nucleotide of the detector primer (Column 4, lines 31-58); extending the primer; and detecting the presence or absence of the single nucleotide polymorphism based on an efficiency of detector primer extension (Column 13, lines 11-34) but they do not teach the detector primer is displaced by extension of a second primer hybridized to the target sequence upstream of the detector primer. However, second primers which upon extension displace a detector primer (i.e. Strand Displacement Amplification (SDA)) was well known in the art at the time the claimed invention was made as taught by Walker et al. Specifically, Walker et al. teach a method similar to that of Newton et al. for detecting a target comprising: hybridizing a detector primer and a second primer to the target such that extension of the second primer displace the detector primer, displacing the detector primer from the target by extension of an upstream primer and amplifying the target (page 1692, Fig. 1) wherein displacement by extension of the second primer generates target sequence of defined 3' and 5' ends with increased efficiency and decreased non-specific primer binding (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detector primer extension of Newton et al. by also extending an upstream primer to displace the detector primer for the expected benefits of increased efficiency and decreased non-specific product formation as taught by Walker et al. (Abstract) to thereby efficiently and accurately detect a single nucleotide polymorphism.

Regarding Claim 56, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using the detector primer i.e. the primer is extended only when the terminal nucleotide of the primer is complementary to the target (Column 12, lines 47-59).

Regarding Claim 57, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using multiple detector primers comprising different diagnostic nucleotides (Column 30, Example 1).

Regarding Claim 59, Newton et al. do not teach the method comprising a second primer. However, Walker et al. teach the similar method wherein the second primer is an amplification

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primer for use in an amplification reaction (page 1692, left column first full paragraph and Fig.

1). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single primer amplification of Newton et al. by also using a second upstream amplification primer for the expected benefit of enhanced amplification of single-stranded or double-stranded targets as taught by Walker et al. (page 1695, left column, last paragraph-right column first paragraph).

Response to Arguments

4. Applicant argues that Newton and Walker do not each the claimed invention because Newton specifically teaches a diagnostic nucleotide of the detector primer be the 3' terminal nucleotide. The arguments have been considered but are deemed moot in view of the amendments, withdrawn rejections and new ground for rejection. However, the arguments are addressed as they apply to the above rejection.

As Applicant noted, Newton teaches the importance of complementarity between the 3' end of the primer and target sequence for the primer extension reaction of Newton to work. The diagnostic primers of Krausa are polymorphic-site specific. Their primers comprise a diagnostic nucleotide one to four nucleotides from the 3' end of the primer wherein upon complementary binding between the target and 3' end of the diagnostic primer, the primer is extended thereby identifying the presence of the polymorphism. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the diagnostic nucleotide and diagnostic primer taught by Krausa et al to the diagnostic primers of Newton et al and to design diagnostic primers having a diagnostic nucleotide about one to four nucleotides from the 3' terminal of the diagnostic primer based on known locations of a polymorphism as taught by Krausa et al for the obvious benefits of polymorphism-specific detection and complete polymorphism mapping as taught by Krausa et al (page 38, left column, lines 8-20).

5. Claims 6 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696) as applied to Claims 1 and 55 respectively above and

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further in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Mullis et al. (U.S. Patent No. 4,683,195, issued 28 July 1987).

Regarding Claims 6 and 58, Newton et al. teach the method wherein the detector primer has a 5' tail sequence (Column 11, lines 40-45) and Walker et al. teach the similar method wherein the detector primer has a 5' tail sequence (page 1693, left column last paragraph) but Newton et al. and Walker et al. do not teach each of the multiple primers has a different 5' sequence. Reynolds et al. teach a similar method for detecting a single polynucleotide polymorphism comprising a detector primer wherein the detector primer has a 5' tail sequence and wherein the 5' tail sequence facilitates cloning and sequencing as taught by Mullis et al. (Column 11, lines 21-27) and Mullis et al. teach multiple primers comprise a different 5' tail sequence to facilitate cloning and sequencing of individual amplified products (Column 15, lines 38-47). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' tail sequence of the detector primers taught by Newton et al., Walker et al. and Reynolds to provide each detector primer with a different 5' tail sequence for the expected benefit of facilitating cloning and sequencing of individual amplified products as taught by Mullis et al. (Column 15, lines 38-47) to thereby simplify identification of individual single nucleotide polymorphic loci.

Response to Arguments

6. Applicant argues that for the reasons stated above regarding Claims 1 and 55, one of skill in the art would not find Claims 6 and 58 to be obvious. The arguments have been considered but are not found persuasive as addressed above regarding Claims 1 and 55.

7. Claims 20, 21, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696) as applied to Claim 1 above and further in view of Chen et al. (Nucleic Acids Research, 1997, 25(2): 347-353).

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Regarding Claims 20, 21, 60 and 61, Newton et al. teach the method wherein the presence or absence of the single nucleotide polymorphism is detected by means of a label associated with the detector primer, wherein the label becomes detectable upon extension of the detector primer (Column 8, lines 13-23) but they do not teach the label is a fluorescent donor/quencher dye pair (Claims 20 and 60) and they do not teach a change in fluorescence is detected as an indication of the presence of the single nucleotide polymorphism (Claims 21 and 61). However, Chen et al. teach a similar method for detecting a single nucleotide polymorphism comprising hybridizing a detector primer to the target; amplifying the target by extension of the detector primer; and detecting the single nucleotide polymorphism and wherein the single nucleotide polymorphism is detected by a label associated with the detector primer, wherein the label produces a change in signal upon extension of the detector primer and wherein the label is a fluorescent donor/quencher pair and a decrease in donor dye (page 348, right column, first and second full paragraphs). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fluorescence donor/quencher dye pair of Chen et al. wherein a change in fluorescence determines the presence of the single nucleotide polymorphism to the fluorescence detection of single nucleotide polymorphism of Newton et al. for the expected benefits of highly sensitive and specific detection of primer extension product as taught by Chen et al. (page 348, right column, second full paragraph).

Response to Arguments

8. Applicant argues that for the reasons stated above regarding Claims 1 and 55, one of skill in the art would not find Claims 20, 21, 60 and 61 to be obvious. The arguments have been considered but are not found persuasive as addressed above regarding Claims 1 and 55.
9. Claims 22 & 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Walker et al. (Nucleic

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Acids Research, 1992, 20(7): 1691-1696) as applied to claim 1 above, and further in view of Thomas et al. (U.S. Patent No. 6,025,130, filed 23 May 1996). Newton et al. teach the method wherein a single nucleotide difference is detected in a target sequence but they do not teach a single nucleotide difference in the HFE gene is detected. However, the HFE i.e. Hereditary Hemochromatosis gene (HH) was known to have a single nucleotide difference in exon 4 as taught by Thomas et al. (Column 11, lines 56-59 and Column 16, lines 59-65). Thomas et al. teach a single nucleotide difference i.e. mutation in exon 4 of the HH gene i.e. 24d1 (Column 16, lines 25-33) wherein the difference is responsible for the majority of hereditary hemochromatosis (Column 11, lines 63-64) and they teach primers for target-specific detection of the 24d1 difference (Column 17, lines 1-4 Fig 6A). Therefore, it would have been obvious to one of ordinary skill in the art to apply the target-specific detection of Newton et al. and Walker et al. to the HFE-specific primer and target sequences taught by Thomas et al. for the expected benefit of efficient gene-based diagnosis of disease-causing mutation i.e. known mutations in the HFE gene.

Response to Arguments

10. Applicant argues that for the reasons stated above regarding Claims 1 and 55, one of skill in the art would not find Claims 22 and 23 to be obvious. The arguments have been considered but are not found persuasive as addressed above regarding Claims 1 and 55.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Conclusion


12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
March 21, 2002


W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600